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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/143,155	08/28/98	DITULLIO	P	10275/045002

HM32/1004

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1632	9

DATE MAILED: 10/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/143,155	DiTullio et al.
Examiner	**Group Art Unit**
Gai (Jennifer) Mi Lee	1632

☒ Responsive to communication(s) filed on *Jun 23, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1, 2, and 6-18* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, and 6-18* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Arguments

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Cancellation of claims 3-5 and 8 without prejudice and claims 1-2, 6-7 and 9-11 are amended, and new claims 12-18 are added in Paper No. 6 filed June 23, 2000.

Claims 1-2, 6-7 and 9-18 are currently pending in the instant application.

This application contains sequence disclosures that are encompassed by the definition s for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Application. Until these requirements are satisfied, the applicant remains in non-compliance with the sequence rules. Please refer to the attached notice to comply.

Information Disclosure Statement

The information disclosure statement filed April 6, 2000 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered.

Double Patenting

Rejection of claims 1-11 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,843,705 is maintained. It is acknowledged that the terminal disclaimer along with the response was received on June 23,

2000 in Paper No. 8. However, a check of $110 was not enclosed for the required fee pursuant to 37 CFR § 1.20(d). No fees have been currently charged for the terminal disclaimer.

Claim Rejections - 35 USC § 112

Rejection of claims 1-11 and newly added claims 12-18 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antithrombin III having a specific glycosylation pattern and obtained from transgenic goat milk, does not reasonably provide enablement for any antithrombin III having any glycosylation differences and obtained from any transgenic mammal is maintained for the reasons of record.

Applicant argues that the specification provided guidance that transgenic mammals other than goat would produce the claimed monosacchride composition and that specification describes the production of both transgenic goats and transgenic mice using the same transgene. In particular, Applicants argues that at page 8, lines 4-22, the specification describes the production of transgenic mice by microinjection of the B6C transgene which is the same transgene used to produce the transgenic goat. Applicant argues that ATIII produced in the mammary gland of such mammals has the claimed monosaccharide composition i.e., a monosaccharide composition including GalNAc, which lacks O-linked glycosylation, which is partially sialylated, and/or which has a sialic acid which includes NGNA. Applicant's arguments have been considered, but are not deemed persuasive.

Applicant's specification does not provide any guidance to the artisan on the phenotypic outcome of the antithrombin III produced by the transgenic mouse or any other mammal as broadly claimed. Applicant's specification supports that the N-linked glycosylation for tgATIII was much more heterogeneous than phATIII, which a higher degree of fucosylation and more varied sialylation (page 19 and Table 3), for example. Applicants argues that at page 8, lines 4-22, the specification describes the production of transgenic mice by microinjection of the B6C transgene which is the same transgene used to produce the transgenic goat. There is no evidence of record which supports that transgenic mice microinjected with a 14.95 Kb transgene (Bc6) into mouse embryos and transgenic goat produced by the same 14.95 Kb transgene (Bc6) would produce the same antithrombin III glycosylation pattern protein. Although the specification compares the antithrombin III produced by the transgenic goat with the plasma derived hATIII, there is no evidence that the transgenic mouse results in the same phenotypic outcome when different patterns of glycosylation is observed between human and transgenic goat derived antithrombin III.

As stated in the previous Office Action, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species. The observation is further supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins et al. state that "a given construct may react very differently from one species to another." See page S39, Summary. Cole et al (1994) J. of Cellular Biochemistry Suppl.. Vol.

0 (18 D) p 265 disclose that NGNA and NANA acid were found on both therapeutic proteins (antithrombin III and LA-tPA), NGNA therefore appears to be a function of expressing the protein in goats. Given such species differences in the expression of a transgene, one of skill in the art would have been required to undergo undue experimentation to determine which promoter, enhancer, intron, exon, and transgene construct would produce the desired phenotype in any and all mammals.

The intention of the animal model, as defined in the specification of the instant application, is for transgenically producing antithrombin III in goats' milk comprising monosaccharides having a specific glycosylation pattern. The claims reads on any glycosylation pattern of antithrombin III that differs from that found in human plasma, but the specification only teaches specific glycosylation patterns of a goat produced antithrombin III. Given such a distinction in glycosylation pattern to host in the expression of antithrombin III, it would require undue experimentation to generate a general model that exhibits all the glycosylation pattern seen in any transgenic mammal or any glycosylation pattern of antithrombin III. It is standardly and well known in the art that glycosylation patterns are a function of the host cell in which the protein product is translated and post-translationally modified by the host enzymes. There is insufficient objective evidence provided to indicate that the numerous embodiments of different glycosylation patterns now claimed would be predictably obtainable from a goat host or any other host. In Drohan review (1997), "The past, present, and future of transgenic bioreactors" supports the specification by stating that the carbohydrate composition and structure of transgenic proteins

may differ from that of their human counterparts. Drohan continue further by disclosing the site-specific addition of oligomannose to specific asparagine residues of recombinant antithrombin III was also observed in the goat mammary gland. However, Drohan concludes away from the claimed invention in stating that these species- and protein- specific glycosylation patterns may affect therapeutic efficacy, binding to cellular receptors and clearance of the recombinant proteins in patients. The specification is only enabling for a transgenic goat comprising monosaccharide compositions of GalNAc; having a monosaccharide composition which comprises GalNAc and which lacks O-linked glycosylation; partially sialyated; sialic acid which includes NGNA; and produced in the mammary glands of only a transgenic goat. The specification does not reasonably provide enablement for a general model because the specification fails to teach such embodiment to any transgenic mammal of the claimed invention. It is noted that the specification must teach those skill in the art how to make and use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). In the instant case, there is no evidence of record which suggests that the mouse transgenically produced antithrombin III would have the same glycosylation pattern as compared to the transgenic goat or in any mammalian species as embraced by the claims. Thus, the evidence of a transgenic mouse without the phenotypic outcome of the antithrombin III produced by the transgenic goat is not sufficient to enable any and all mammal. Therefore, it would have required undue experimentation for the skilled artisan to determine how to make antithrombin III with specific glycosylation pattern produced by the

transgenic goat in any mammal, due to the unpredictability of the phenotypic outcome of antithrombin III and the lack of guidance provided by the specification. Therefore, for the reasons stated above and in the Office Action mailed December 21, 1999, paper #5, the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The prior rejection of claims 1,2,7,8 and 11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicant's amendment to the claims filed June 23, 2000.

Claim 18 is vague and indefinite for its recitation of "faster clearance time" because it is unclear from the specification as to what is encompassed in the claims as to how fast is faster. The metes and bounds of the claim cannot be determined.

Claim Rejections - 35 USC § 102

The prior rejection of claim 5 under 35 U.S.C. 102(a) as being clearly anticipated by Edmunds et al (1994) J. of Cellular Biochemistry Suppl., Vol. 0 (18D) p. 265 is withdrawn in view of applicant's amendment canceling claim 5 in Paper No. 6 filed in June 23, 2000.

The prior rejection of claims 1, 4,6-7 and 1, as originally filed or newly amended, under 35 U.S.C. 102 (a) as being clearly anticipated by Cole et al (1994) J. of Cellular Biochemistry Suppl.. Vol. 0 (18 D) p 265 is maintained for the reasons of record.

As to the discussion of the Cole declarations under 37 C.F.R. 1.132, both declarations are ineffective under In re Katz because the two declarations remove the names of Higgins, Bernasconi, Gerone, and Edmunds leaving only author Cole. Cole alone, is not identical to the inventive entity of DiTullio, Meade and Cole and is legally another to the present inventive entity. The In re Katz is further insufficient in that it does not clearly state DiTullio and Meade contribution to the inventive concept of the claimed invention.

Cole et al teach the glycosylation patterns and the production of therapeutic proteins (antithrombin III) in the milk of transgenic animals (transgenic goat milk) can be achieved at very high expression levels compared to tissue culture. Cole et al further discloses the substitution of GalNAc for Gal due to the function of expressing the proteins in the mammary gland and not a species difference as goat plasma ATIII does not contain this substitution. The transgenic proteins are more fucosylated and less sialylated than their recombinant or plasma counterparts. NGNA and NANA acid were found on both therapeutic proteins, NGNA therefore appears to be a function of expressing the protein in goats. Thus, Cole et al clearly anticipates claims 1, 4, 6-7 and 10.

Cole et al does not teach transgenically produced antithrombin III comprising a monosaccharide composition which includes: lacks O-linked glycosylation, nor the transgenic method for producing antithrombin III in a mammal, specifically. What Cole et al failed to disclose in his abstract are **inherent** to the claimed invention of the applicant for those

encompassed characteristics of monosaccharide composition in relation to glycosylation patterns and/or positions of the monosaccharides.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gai (Jennifer) Mi Lee, whose telephone number is 703-306-5881. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (EST). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on 703-305-6608. The FAX phone numbers for group 1600 are 703-308-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Gai (Jennifer) Lee
Patent Examiner
Art Unit 1600

Karen M. Hauda

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